

# Clinical review

## *Clostridium difficile* associated diarrhoea: diagnosis and treatment

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While John Starr was working as a senior registrar at the Hammersmith Hospital in London, an upsurge in episodes of *Clostridium difficile* associated diarrhoea seemed to be associated with increasing use of third generation cephalosporins. This article seeks to clarify some of the diagnostic problems and help with appropriate treatment of this condition.

*Clostridium difficile* associated diarrhoea is a serious condition with a mortality of up to 25% in frail elderly people.<sup>1</sup> It affects older, frailer, hospitalised patients and also younger patients who are immunosuppressed.

Cross infection by *C difficile* is common in neonatal units, but neonates do not seem to develop *C difficile* associated diarrhoea.

The diagnosis of *C difficile* associated diarrhoea depends on:

- Presence of diarrhoea, defined as an increase in stool liquidity usually accompanied by an increased frequency of bowel motions. A formal cut-off is the passing of more than 300 ml of liquid stool in 24 hours
- Detection of toxins produced by *C difficile* in the stools.

The patient may also experience abdominal pain and have systemic features of malaise, fever, dehydration, and delirium. A pseudomembranous colitis is present in severe cases. In this state there is sloughing of the colonic epithelium, which is severely inflamed due to the cytotoxic action of *C difficile*.

*C difficile* associated diarrhoea is classically associated with clindamycin, but it may occur after exposure to a wide range of antibiotics.

Symptoms usually start during antibiotic treatment or shortly afterwards. Symptoms can be delayed by a few weeks, so it is worth asking patients whether they are currently taking, or have recently taken, antibiotics.

### How does it happen?

*C difficile* is spread by the faecal-oral route, albeit indirectly through spores left on surfaces. *C difficile* is an anaerobic, Gram positive, spore forming bacterium that is the major identifiable cause of antibiotic associated diarrhoea.

- The prevalence of asymptomatic colonisation in the community is less than 5%<sup>2–4</sup>
- The prevalence of asymptomatic colonisation in hospital, especially in older people, is higher at over 20%.<sup>5–7</sup>

In a proportion of those colonised, perhaps around one third,<sup>7</sup> *C difficile* produces toxins that cause diarrhoea. The two principal toxins, A and B, share

63% of amino acid sequence homology and act on small GTP-binding proteins (these are part of the large family of guanine nucleotide binding proteins that are coupled to many membrane receptors and are implicated in many diseases).

Toxin B is around 1000 times more cytotoxic than toxin A.<sup>8</sup> Toxin A is also an enterotoxin in that it loosens the tight junctions between the epithelial cells that line the colon, which helps toxin B enter into epithelial cells.

Some strains also produce a binary toxin, but its role in human disease is uncertain.<sup>9</sup>

*C difficile* associated diarrhoea is therefore characterised by a progression from an uncolonised state, through to *C difficile* colonisation, followed by toxin production. In part this depends on the specific strain of *C difficile*, with one strain (toxigenic S-type 5236) responsible for around 70% of cases in the UK.<sup>6</sup> However, host factors that predispose to colonisation and toxin production are equally important.

One systematic review identified several risk factors for *C difficile* associated diarrhoea<sup>10</sup>:

- Increasing age (excluding infancy)
- Severe underlying disease
- Non-surgical gastrointestinal procedures
- Presence of a nasogastric tube
- Receiving anti-ulcer medications
- Stay on intensive care unit
- Long duration of hospital stay
- Long duration of antibiotic course
- Receiving multiple antibiotics.

Another systematic review identified clindamycin, cephalosporins, and penicillins as the classes of antibiotics most associated with *C difficile* associated diarrhoea.<sup>11</sup>

One study found that the risk factors for colonisation in a medicine of the elderly hospital (age, admission from another hospital, use of non-cephalosporin and cephalosporin antibiotics) were different from the risk factors for the transition between culture-positive and toxin-positive status (antibiotic use only).<sup>12</sup>

A failure to mount an immune response is associated with colonisation and toxin production.<sup>13 14</sup>

In addition, the case mix on wards, and bays within wards, is important because of a potential herd immunity effect that can prevent epidemic outbreaks of *C difficile* associated diarrhoea.<sup>15</sup> For example, if only a few patients on a ward have been exposed to antibiotics, most of those who have not been treated with antibiotics will retain their normal colonic bacterial flora and will not develop *C difficile* associated diarrhoea.

For an outbreak to occur, each case of *C difficile* associated diarrhoea must give rise to more than one new case. This depends not only on the infectivity of the agent, in this case *C difficile*, but also on the proportion of surrounding patients who are susceptible to infection. So as the proportion of patients on the ward who have received antibiotics and who are old rises, a threshold is reached where the product of the infectivity of *C difficile* and the proportion of susceptible patients is greater than one, and an outbreak of *C difficile* associated diarrhoea occurs.

Infectivity depends not just on the characteristics of the specific strain, but on factors that impact on cross infection (hygiene, bed spacing, and shared toilet facilities).

## How should I treat it?

Treatment can be divided into:

- Therapy for patients with *C difficile* associated diarrhoea
- Measures to prevent other patients developing it.

### Patients with *C difficile* associated diarrhoea

Therapy for patients with *C difficile* associated diarrhoea comprises:

- Supportive measures (adequate fluid and electrolyte replacement)
- Withdrawal of current antibiotic therapy if possible
- Antibiotic treatment to eradicate *C difficile*.

Standard first line antibiotic therapy is metronidazole 400 mg administered orally three times a day. An alternative is oral vancomycin 125 mg four times a day, or at a higher dose for severe episodes. One study suggested this should be used as first line treatment for patients with albumin <25 g/l or for patients who are in intensive care.<sup>16</sup> Resistance to metronidazole and vancomycin is not reported, but changing antibiotic is often tried empirically after one week if symptoms have not resolved.

Placebo arms in clinical trials suggest that *C difficile* associated diarrhoea will resolve without antibiotic therapy in around 20% of patients. An earlier systematic review found that metronidazole and vancomycin produced comparable results.<sup>17</sup>

If a patient can't take oral medications, a nasogastric tube will be needed to administer antibiotics because an enteral route is required to treat the infection.

Evidence is inadequate to support the use of prebiotics (nutrients that encourage "normal" colonic bacterial flora) or probiotics (live microbial supplements, for example containing bifidobacteria, lactobacilli, and so on) for treating patients with established *C difficile* associated diarrhoea.<sup>18</sup>

### Preventing *C difficile* associated diarrhoea

Prevention of *C difficile* associated diarrhoea consists of general infection control measures and those more specific for *C difficile*.

Diagnosis now tends to be made by detecting toxin, and so laboratories no longer culture *C difficile*. This hampers wider public health control of outbreaks and monitoring of antibiotic sensitivities because there may be a delay in detecting emerging epidemic strains.<sup>19</sup> It also impairs diagnostic evaluation because cytotoxin is absent from the stools of a small proportion of endoscopically proved cases.<sup>20</sup>

Each unit should evaluate its case mix and, therefore, its risk of an outbreak of *C difficile* associated diarrhoea. For those at high risk, strict control of antibiotic prescribing may be useful.<sup>21</sup>

One study showed that several measures significantly reduced the incidence of *C difficile* associated diarrhoea<sup>22</sup>:

- Revision and enforcement of the isolation policy to include wearing of gloves and gowns, and hand washing by healthcare staff; patients isolated in single or double bedded rooms or cohort bays; equipment such as thermometers and stethoscopes dedicated to each patient
- Monthly educational programme for all healthcare workers
- Phenolic disinfectant used for environmental cleaning
- Triclosan (0.03%) soap used for hand washing
- Sterilisation department centralised
- Cart washer installed for cleaning wheelchairs and stretchers that have not come into direct contact with patients
- Aggressive surveillance activity.

Evidence is poor for routine hand cleansing and evidence is weak for environmental disinfectant cleansing.<sup>23 24</sup> Nevertheless, such interventions are likely to be as important as antibiotic control.<sup>25</sup>

Probiotics are probably effective in preventing recurrence of *C difficile* associated diarrhoea,<sup>26</sup> but the evidence for primary prevention, even in targeted populations, is equivocal.<sup>18 27</sup>

## Recurrence

Recurrence can occur in up to one third of cases. It is sometimes difficult to determine whether this is due to failure of eradication of *C difficile* and subsequent recolonisation with normal colonic bacterial flora, or to a new infection of a susceptible patient. Strain typing may help, but its use is limited because the "epidemic" strain accounts for around 70% of infections, and colonisation with more than one strain is not uncommon.

It is not unusual for an initial episode of *C difficile* associated diarrhoea to affect the patient's nutritional

### Clinical tips

You should treat patients whose stools contain a positive culture but do not contain toxins only if you strongly suspect that they have *C difficile* associated diarrhoea and if they are systemically unwell. This is because *C difficile* may be found incidentally in the stools of patients whose diarrhoea is due to other causes.

Use high dose vancomycin as first line treatment for patients on the intensive care unit or for patients with low albumin levels.

status and for the serum albumin to remain low at the time of recurrence. This is an indication to use high dose vancomycin.

## Vaccines

A report to the Department of Health in 2004 on appropriate public health surveillance of *C difficile* reviewed current research.<sup>28</sup> Key themes were infection control, antibiotic restriction policies (especially of third generation cephalosporins), and use of probiotics. It also noted that vaccines against *C difficile* toxins have been successful in animal models and that early safety trials in humans have been satisfactory. However, active immunisation may not be effective in people most at risk of *C difficile*, who characteristically fail to mount an immune response to *C difficile* infection.

Moreover, local colonic immunoglobulin A (IgA) production may be more important in protecting against *C difficile* associated diarrhoea than humoral IgG, and colonic IgA production is impaired in

## Sample questions

Here is a small sample of the questions that you can find at the end of this module. To see all the questions and to get the answers, go to [www.bmjlearning.com/](http://www.bmjlearning.com/) and search for "clostridium difficile"

1. A 79 year old man in a nursing home has mild diarrhoea and his stool samples are positive for *C difficile* toxin. He is otherwise well. Which of the following treatments would you give him?
  - a. He should be given probiotics
  - b. He should be treated with metronidazole 400 mg by mouth three times a day
  - c. He should be treated with vancomycin 250 mg four times a day
2. A 70 year old woman on ITU develops severe diarrhoea, abdominal pain, pyrexia, and delirium. Stool samples are culture-positive for *C difficile*, but toxin is not detected. What should be the first step in her management?
  - a. She should be treated with vancomycin 250 mg four times a day
  - b. She should be treated with metronidazole 400 mg three times a day
  - c. She should be treated expectantly, and antibiotics started only if her stools become toxin positive
3. A 75 year old man is found to have *C difficile* in his stools. But he is asymptomatic and there are no toxins in his stools. What should you advise?
  - a. Start metronidazole
  - b. Start vancomycin
  - c. Observe him off treatment
4. In what proportion of people who are colonised with *C difficile* does the bacterium produce toxins that cause diarrhoea?
  - a. 10%
  - b. 30%
  - c. 60%
5. You diagnose a 65 year old man with *C difficile* associated diarrhoea. You want him to start metronidazole, but he is unwilling and asks whether his symptoms could resolve on their own. What percentage of patients with *C difficile* associated diarrhoea will get better without antibiotic therapy?
  - a. About 20%
  - b. About 50%
  - c. About 80%

## Summary points

*Clostridium difficile* associated diarrhoea is the most common cause of antibiotic associated diarrhoea in hospital

Oral metronidazole 400 mg three times a day and vancomycin 125 mg four times a day are the treatments of choice. You should usually continue treatment until symptoms stop

Probiotics may be useful for preventing recurrence

Evidence for the effectiveness of infection control measures is limited

patients with *C difficile* associated diarrhoea.<sup>29</sup> In view of this, passive immunisation, for example with pooled human immunoglobulin, may be a more promising strategy.<sup>30</sup>

In the meantime, clinicians will need to weigh the possible advantages of using vancomycin first line, especially at high dose, against the potential problems of inducing greater vancomycin resistant enterococci.<sup>1</sup>

## Models and analysis

Looking to the future, one of the major difficulties is applying randomised controlled trial methodology to studying a condition that depends on herd immunity and for which there are many known confounding variables. These "herds" are spatially and temporally discrete but, in general, the number of cases of *C difficile* associated diarrhoea within a herd is too small for a randomised controlled trial. Mathematical modelling is therefore an alternative.

One promising approach is to apply stochastic models (models that deal with small numbers of chance events) to observational data.<sup>31</sup> Such random stochastic events can be simulated by Monte Carlo methods. However, events are linked spatially and temporally and are therefore not individually independent.

Fortunately, mathematical methods such as Markov chain models can be used. These were developed to understand paths of cosmic particles as they collide with atoms on entering the earth's atmosphere. These models can help us conduct research on patients with *C difficile* associated diarrhoea.

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## Lesson of the week

### Paralytic rabies after a two week holiday in India

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Rabies is an acute infection of the central nervous system (CNS) and caused by rabies virus or related members of the genus *Lyssavirus*, family Rhabdoviridae.<sup>1</sup> The virus is usually transmitted through a dog bite and produces one of the most important viral encephalitis worldwide, with at least 40 000 deaths reported annually.<sup>2</sup> However, it is rare in the United Kingdom, where just 12 cases have been reported since 1977<sup>3</sup>: 11 were imported from overseas, and one occurred in a bat handler infected in Scotland with European bat lyssavirus type 2a.<sup>4</sup> Most UK patients presented with furious rabies, which is characterised by hydrophobia and spasms. We report a case of paralytic rabies in a tourist after a two week holiday in Goa, India.

#### Case report

A woman in her late 30s was admitted to her local general hospital under the orthopaedic surgeons, with lower back pain radiating to the left leg. The pain had started four days earlier, was severe and shooting in nature, and was getting worse. She had been seen twice in casualty in the preceding days, and by the time of admission she was unable to walk. She also had a headache and had vomited once. Three and a half months before admission, during a two week holiday to Goa, India, she had been bitten by a dog; she was walking in the street when a puppy on a lead nipped her on the

left leg. There was a slight graze, which she wiped with a tissue, but she did not seek further medical help. Her family reported that she was not aware of the risk of rabies and had not received any pre-exposure or post-exposure vaccination. She had also had intermittent diarrhoea for the past four months, which preceded her trip to India, but gastroscopy and flexible sigmoidoscopy on return from India were normal. On examination she had a temperature of 38.5°C. The left leg, which was extremely painful and required morphine, was areflexic and weak, with sensory loss in L4-S1 dermatomes. She had leucocytosis. A computed tomography scan of the spine looking for a prolapsed disc was normal. Over the next few days she developed a sore throat and had difficulty swallowing, a swollen left eyelid, a goose pimple rash on her skin, and marked bilateral loss of hearing. On day 8 the patient was referred to the medical team, which noted that she was now lethargic and had flaccid weakness in both legs and arms. A provisional diagnosis of Guillain-Barré syndrome was made, and she was treated with intravenous immunoglobulin. A lumbar puncture found clear cerebrospinal fluid with a white cell count of 11 cells/μl (9 lymphocytes, 2 polymorphonuclear



Editorial by  
Pounder

**A history of a dog bite from a rabies endemic country should always be taken seriously**

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Further details about figure 2, Genbank accession numbers for the strains of virus, and a supplementary figure, showing hemi-nested reverse transcriptase-polymerase chain reaction on diagnostic samples and serological results, are on bmj.com